AMENDMENTS TO THE DRAWINGS:

After FIGURE 6, please insert FIGURE 7. (Attachment 1).

REMARKS

Applicant thanks the Examiner for agreeing to a personal interview to better describe the instant invention. During the interview conducted on March 28, 2007, it was agreed that the limitation requiring that the siRNA bind the target mRNA at least 9 bp downstream of the transcription start site should be removed. Reconsideration of the other claims in above-identified application is respectively requested in view of the above amendments and the following remarks.

STATUS OF THE CLAIMS

Examiner objected to claims 1, 24, and 85 and rejected claims 1, 10, 14, 24, 25, 86, 87, and 89 for multiple reasons. Claims 85 and 88 are canceled without prejudice. Claims 5, 9, and 19 have been previously canceled. Claims 90-98 have been added. Claims 1-4, 6-8, 10-18, 20-84, 86-87, 89-98 are now pending. Claims 1 and 24 have been amended. Claims 2-4, 6-8, 11-13, 15-18, 20-23, 26-84 are withdrawn. Claims 1, 10, 14, 24, 25, and 86, 87, and 89-98 are currently under consideration.

The support for the amendment to claim 1 and the newly added claim 90 can be found in the original claims and specification as described in details below. The support for the newly added claims 91-97 is found in claims 10, 14, 24, 25, and 86, 87, and 89 and page 29 of the specification. The support for claim 98 is in the original claim 88.

AMENDMENTS TO THE SPECIFICATION AND CLAIMS

The pages 9, 14, 29-35 of the Specification have been amended to incorporate material from a U.S. Application SN 09/872,698 and also correct minor formatting and spelling errors. This Amendment adds no new matter to the application as filed on November 25, 2003.

Pursuant to 37 CFR § 1.57, incorporated information from another U.S. patent application is as much a part of the application as filed as if the text was repeated in the application. Therefore, such information should be treated as part of the text of the application as originally filed. Replacing the identified material incorporated by reference with the actual text is not new matter. (see MPEP § 2163.07(b)).

Consistent with the Rule, Applicant also makes the statement that "the material being inserted into the specification is the material that previously incorporated by reference from US Application SN 09/872,698 at page 29 of the instant specification and

that the amendment contains no new matter." (*see* Attachments 2 and 3 for marked up and replacement sheets).

Support for the newly added claims are found in the incorporated material. Specifically, the support for the limitations articulated in the step (b) of claim 90 is in the incorporated Application SN 09/872,698; filed on June 01, 2001, issued as US Patent 7,189,222 ("the '698 Application" see Attachment 5) on March 13, 2007, and as originally incorporated by reference in the instant specification. (see the Specification at page 29, line 18).

Figure 7 of the '698 Application has been incorporated in the instant application in compliance with 37 CFR §§ 1.121 and 1.184. The support for the newly added limitations is found at Figure 7; page 5, lines 29-30; page 11, lines 9-15, 22-29; and page 12, lines 1-10 of the '698 Application. Accordingly, this Amendment adds no new matter to the instant application as filed on November 25, 2003.

Claim 90 is added to address Examiner's concerns and Applicant's position as articulated during the interview. In doing so, Applicant has merely made explicit what has been implicit and inherent in the original application by incorporating the language directly from the '698 Application. Applicant believes that the presented claims are free of prior art and therefore patentable.

SUMMARY OF THE INVENTION

Applicant's invention is directed to *inter alia* a medical system for treating a spinocerebellar ataxia type 1 in a human live patient comprising: (a) an intracranial access device; (b) a patient-specific intra-operative mapping means for locating a predetermined intraparenchymal location in the brain of the patient, said location comprising neurons natively expressing a gene encoding an ataxin-1 protein; (c) a deliverable amount of a small interfering RNA capable of reducing the amount of ataxin-1 protein produced in said neurons, or a vector encoding said small interfering RNA, wherein said small interfering RNA has a length of between about 15 and about 30 nucleotides; and (d) a delivery means for delivering said small interfering RNA or vector encoding said small interfering RNA to said location of the brain of said patient from said intracranial access device through a stereotactically implanted catheter comprising a material which does not interfere with intra-operative brain imaging.

In another aspect, the invention provides a medical system for treating spinocerebellar ataxia type 1 in a human patient comprising: (a) an intracranial access device comprising a material which does not interfere with intra-operative brain imaging; (b) a patient-specific mapping means for allowing stereotactical implantation of the device in a predetermined location in the brain of the patient, said location comprising cells natively expressing a gene encoding an ataxin-1 protein; (c) a deliverable amount of a small interfering RNA capable of reducing the amount of ataxin-1 protein produced in said cells or a vector encoding said small interfering RNA; and (d) a delivery means for delivering said small interfering RNA or vector encoding said small interfering RNA to said location of the brain of said patient from said intracranial access device through a stereotactically implanted catheter.

The pending claims rather than relying on pre- or post- surgical mapping or imaging techniques of a patient's brain, employs such imaging procedures as guided stereotactical and triangulation techniques *during the actual brain surgery* to enhance delivery of siRNA to the locations of interest.

Of course, equivalents to the system disclosed in the specification are possible. For example, verification of the placement of the distal end of the catheter may be performed intra-operatively by MRI, using an intra-operative MR image-guidance system such as the PoleStar® iMRI Navigation Suite or a comparable system.

In another example, a means for locating the distal end during the access and location process is by use of small infrared light-reflective spheres temporarily attached to the proximal portion of the catheter or the surgical instrument that the surgeon is using to insert the catheter into the patient's brain. An infrared camera in the operating room positioned near the operating table emits and tracks infrared signals reflecting off these small spheres. The detected reflection then enables a software and computer system (such as the StealthStation®) to compute and display the position of the catheter's distal end superimposed on previously captured MRI images of this specific patient, intra-operatively, in real-time. (This is possible because the distal end of the catheter is a known linear distance from the proximal portion of the catheter to which the infrared light-reflective spheres have been temporarily attached).

In another example, a means for locating the distal end during the access and location process is by use of infrared-emitting light emitting diodes (LEDs) temporarily attached to the proximal portion of the catheter or the surgical instrument that the surgeon is using to insert the catheter into the patient's brain. An infrared camera in the operating room positioned near the operating table detects the infrared beams emitted from these LEDs. These detected beams enable a software and computer system (such as the StealthStation®) to compute and display the position of the catheter's distal end superimposed on previously captured MRI images of this specific patient, intra-operatively, in real-time. (This is possible because the distal end of the catheter is a known linear distance from the proximal portion of the catheter to which the LEDs have been temporarily attached).

Regardless of whether passively reflected infrared light or actively emitted infrared light is utilized for computing the position of the catheter or the surgical instrument that the surgeon is using to insert the catheter into the patient's brain, the goal of utilizing infrared triangulation is to enable the operator to accurately detect the precise location of the tip to facilitate placement and intra-operative verification of the integrity and position of distal end of catheter.

RESPONSE TO THE OFFICE ACTION ISSUED JANUARY 5, 2007

NON-COMPLIANT AMENDMENT

Applicant had made all efforts to clarify the amendments hereby presented and address Examiner's concerns. Applicant believes that the instant amendments comply with 37 CFR § 1.121(c)(4)(i). Accordingly, this issue is now moot.

CLAIM OBJECTIONS

The Examiner objected to claim 1 asserting that the terms "live" and "patient" are redundant and the term "patient" inherently designates a living system, e.g., a human. Applicant amended claim 1 to remove the term "live" from the claim. Thus, the objection should be withdrawn.

The Examiner also objected to claim 24. Claim 24 is now amended to spell out that the intracranial access port is a part of the intracranial access device specified in claim 1. Accordingly, the objection should be withdrawn.

The Examiner further objected to claim 85 as being an improper dependent claim failing to further limit the scope of the claim it depends from. Applicant cancels claim 85 without prejudice. Accordingly, the objection is moot.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 1, 10, 14, 24, 25, and 85-89 for indefiniteness. Before the instant amendment, claim 1 recited "small inhibitory RNA" without insufficient antecedent basis. The other pending claims were rejected due to their dependence on claim 1. The Examiner correctly pointed out that the recitation appears to be a typographical error. Applicant is grateful to the Examiner for noticing this error. In the newly amended form, claim 1 does not recite "small inhibitory RNA". Accordingly, Applicant respectfully requests that this ground for rejection be removed.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 1, 10, 14, 24, 25, and 85-89 under 35 USC § 112, first paragraph asserting that the requirement that the small interfering RNA should target a portion of SCA-1 mRNA which is at least 9 bp downstream of the transcription start site. Applicant respectfully notes that the specification discloses siRNA sequences which bind a portion of SCA-1 located mRNA more than 9 bp downstream of the transcription start site (e.g., 945-965). Nevertheless, in the interest of the expedited prosecution, the Applicant removed this limitation from claim 1. Accordingly, Applicant respectfully requests the Examiner to withdraw this ground for rejection.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION (PREVIOUS)

The Examiner rejected claims 1, 10, 14, and 25 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 7, 8, 16, 17, and 29 of a co-pending application No. 10/962,732.

MPEP § 804(I)(B)(1) recites as follows:

> [i]f a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

Applicant respectfully notes that the instant application was filed on November 25, 2003, while application No. 10/962,732 was filed later, on October 12, 2004. Therefore, the instant application is the earlier-filed application of the two applications. Applicant further notes that as of May 21, 2007, no action on merits have been taken regarding the later-filed application No. 10/962,732.

Accordingly, without making any admissions or agreeing with the Examiner, Applicant respectfully requests postponement of any action on this ground of rejection until this is the only ground for rejection of either claims 1, 10, 14, and 25 of the instant application or claims 7, 8, 16, 17, and 29 of a co-pending application No. 10/962,732.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION (NEW)

The Examiner further rejected claims 1, 10, 14, 24, 25, 85-87 and 89 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-17, and 29 of a co-pending application No. 10/962,732.

MPEP § 804(I)(B)(1) recites as follows:

> [i]f a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

Applicant respectfully notes that the instant application was filed on November 25, 2003, while application No. 10/962,732 was filed later, on October 12, 2004. Therefore, the instant application is the earlier-filed application of the two applications. Applicant further notes that as of May 21, 2007, no action on merits have been taken regarding the later-filed application No. 10/962,732.

Accordingly, without making any admissions or agreeing with the Examiner, Applicant respectfully requests postponement of any action on this ground of rejection until this is the only ground for rejection of either claims 1, 10, 14, and 25 of the instant application or claims 1- 17, and 29 of a co-pending application No. 10/962,732.

REJECTION ON THE BASIS OF 35 U.S.C. §103

The Examiner has rejected claims 1, 10, 14, 24, 25, 86, 87 and 89 under 35 U.S.C. § 103 as being allegedly unpatentable over Xia et al. (2002) *Nature* 20:1006-1010; Driscoll et al. (WO 01/49844); Cahill et al. (1995) *Atlas of Human Cross-sectional Anatomy,* Wiley-Liss, 3rd ed.; Serra et al. (1996) *Medical Image Analysis* 1(4):317-329; Morel et al. (1997) *J. Comparative Neurology* 387-:588-630; Clark et al. (1997) *J. Neuroscience* 17:7385-7395; Salehi et al. (1999) *J. Neural Transm.* 106:955-986; Whitesell et al. (1993) *Proc. Natl. Acad. Sci.* 90:4665-4669; Davidson et al. (US Patent Application Publication 2004/0023390); Matilla et al. (1998) *J. Neuroscience* 18:5508-5516; Exhibit A: NCBI published mRNA sequence of SCA1 (Mar. 24, 1999) and Caplen et al. (2002) *Human Molecular Genetics* 11: 175-184.

THE REJECTION IS IMPROPER BECAUSE IT DOES NOT TEACH ALL ELEMENTS OF THE CLAIMED INVENTION

During the interview, the Applicant, Dr. W. Kaemmerer, elaborated on the meaning of the term "mapping means" and provided evidence that mapping means described in the references used by the Examiners are unsuitable for the instant invention, i.e., delivering siRNA into a predetermined location of a human patient. Even though simple stereotactic surgery described in the references brought forth by the Examiner may be suitable for locating targets in rodent brains, these means are extremely imprecise and therefore unsuitable for therapy of a relatively large subject (e.g., a sheep or a human). In fact, the mapping means which are necessary for locating a predetermined location in a brain of a human patient and for placing a catheter into this predetermined location are patient-specific and image guided.

Here, the medical system claimed by the Applicant allows neurosurgeons to precisely plan, re-plan and visualize a procedure as it proceeds deep within the brain for treating a neurological disorder such as for example SCA1 in a living human patient. None of the references cited by the Examiner, either alone or in combination disclose or suggest such system especially for siRNA treatment of spinocerebellar ataxia type 1.

Claim 1 has also been amended to recite that the mapping means of the claimed system must be patient-specific and intra-operative. This limitation is neither disclosed nor suggested in the prior art references used by the Examiner, as will be discussed in details below.

Xia, Caplen, Davidson, Driscoll, and Exhibit A disclose siRNA molecules capable of inhibiting artificial mRNA constructs *in vitro* or in a mouse. Some of these references (most notably, Xia) generally disclose stereotactical delivery of siRNA into a brain of a mouse using a mouse brain atlas. They do not disclose or suggest an animal-specific mapping means or the intraoperative imaging. As discussed above, and as was discussed during the interview with the Examiner, an animal specific (as opposed to a species specific) mapping means is crucial for a targeted placement of the catheter into a larger animal (e.g., sheep or human).

Similarly, Cahill discloses a laundry list of structures or their relative locations in the one-size-fits-all mode. Due to the intraspecies variations, Cahill is unsuitable even as the pre-operative planning tool, let alone a patient-specific mapping means.

Clark, Salehi and Matilla do not teach or suggest suppression of the expression of the SCA1 gene in patients as a means of treating the disease. Clark and Salehi specify relationship between certain brain structures and neurodegenerative diseases. Matilla discloses that knocking out SCA1 gene function from embryonic conception does not cause an ataxic phenotype in the developing or adult animal, indicating that the SCA1 disease in humans is not due to a loss of the function of the SCA1 gene or ataxin-1 protein. No suggestion is provided either to explore siRNA technology as a means for doing so or to administer siRNA in the areas endogenously expressing SCA-1. Finally, Clark, Matilla or Salehi do not disclose or suggest intra-operative patient specific mapping means.

With respect to Whitesell, Applicant states that the instant invention is directed to siRNA and not antisense. Whitesell reports that its study supports the feasibility of continuously perfusing the CNS with therapeutic concentrations of intact antisense oligonucleotides, and the possibility of using such therapeutics to target leptomeninigeal and intraparenchymal disease processes (page 4669). Applicant respectfully submits that the instantly amended claims are directed to siRNA and not antisense, which are different technologies, as has been recognized during the prosecution of the instant application.

A second reason that Whitesell is inapposite to the instant invention is that the oligonucleotides used in Whitesell are not the mapping means disclosed in pending claim 1. Claim 1 discloses mapping means to locate a predetermined location in a brain. Thus, the

location in the brain must be determined before the administration of the siRNA treatment, not during or after such treatment. Whitesell simply does not teach this element.

The teachings of Serra and Morel do not remedy the short comings of the discussed references. Accordingly, the combination of Xia, Caplen, Whitesell, Davidson, Driscoll, Exhibit A, Clark, Salehi, and Matilla falls short of making claim 1 obvious at least because such combination of prior art teachings does not meet all elements of the instant claim.

THE REJECTION IS IMPROPER BECAUSE THERE IS NO MOTIVATION, TEACHING OR SUGGESTION IN THE ART TO COMBINE THE REFERENCES

Not only there would have been no motivation in the art at the time to combine a mapping means with a drug delivery during a brain surgery, but also there would not have been any expectation of success even if one of ordinary skill in the art would have combined the cited references).

As none of the references cited references teach intra-operative and patient specific delivery and mapping means, one of ordinary skill in the art would have had no motivation in the art to combine the references and reach the claimed invention. Examiner has relied on Serra and Morel for their teachings of equipments, guides and/or methods for delivery of siRNA. (see also, 2nd ¶, pg. 17)

However, neither Serra nor Morel disclose or suggest the use of any siRNA molecules, let alone the siRNA molecules which can treat spinocerebellar ataxia type 1. In fact, Morel and Serra are silent as to the type of intracranial access device best suited for their methodology. There is absolutely no suggestion as to the use of a delivery device that does not interfere with brain imaging during the procedure.

Examiner appears to use Morel and Serra to establish the predictability of the state of art as to employing other mapping means. However, these disclosures still fall short of the mapping means of the instant invention.

For example, Morel states as follows:

> much progress has been made in stereotactic neurosurgery by the use of computer tomography (CT) or magnetic resonance imaging (MRI)-guided stereotaxy, and preoperative microelectrode recordings for the localization of targets. However, the initial anatomical determination and accurate three-dimensional (3-D) coordinate transfer of the target onto brain images are still impeded by insufficient histological and stereotactic precision of currently available atlases of human thalamus.

Morel at page 598, left column. Essentially, Morel indicates that MRI and CT, along with pre-operative microelectrode recordings, can be used in the pre-operative neurosurgical planning, wherein the target structure is pre-determined by CT or MRI techniques. Yet, even Morel recognizes that such approaches are insufficient for mapping human thalamus. Notably, Morel does not make any references to previous publications when she notes CT or MRI stereotactic surgery. Even taken at a face value, this statement does not disclose or suggest intraoperative mapping means (e.g., visualizing the placement of the catheter into the pre-determined brain location in real time). In fact, Morel's results were obtained from thalamic blocks of cadavers, which is clearly not the object of the instant invention.

Serra also falls short from fully addressing the above-specified elements. More specifically, Serra discloses "a surgical planning system." Serra at page 318, top of left column, emphasis added. Further, Serra states as follows:

> [a] stereotactic procedure is usually performed in several stages (see Figure 6): (i) frame fixation along with planning; (ii) linking information from the scan(s), anatomical references and stereotactic models; (iii) computerized neurosurgery planning and (iv) neurosurgery. The Brain Bench [the most comprehensive system disclosed in Serra] addresses (i), (ii), and (iii).

Serra at page 321, bottom of right column. The label "Intra-operative data" in Figure 6 of Serra only reflects the data associated with the placement of the stereotactical frame (Fixation device) prior to the surgical access of the pre-determined location in the patient brain. Serra does not address image-guided placement of the catheter that is of a material which does not interfere with intra-operative brain imaging. Therefore, Serra's system is also not useful for intra-surgical applications in brain.

At most the combined teachings of the references would suggest a blinded approach to a precision-vital neurosurgical procedure, endangering the life of the patient in need of such treatment. Such approach is not a risk that one of ordinary skill in the art, namely a surgeon, would be willing to take. Therefore, there is no motivation to combine Serra and Morel with the combination of Xia, Caplen, Whitesell, Davidson, Driscoll, Exhibit A, Clark, Salehi, and Matilla. Applicant respectfully requests withdrawal of the rejection.

EXAMINER'S INTERVIEW

Applicant noticed during the interview that Examiner's positions presented in this case is inconsistent with the art unit's policy and the state of art. During the interview conducted on March 28, 2007, Dr. Kaemmerer demonstrated that a supposition that the atlas-based mapping means of the prior art is sufficient for delivery of the therapeutic into the pre-determined location in a brain of a human patient is simply false, because it does not provide the precision necessary during such procedures. One of ordinary skill in the art being in possession of the instant invention can appreciate the level of accuracy provided for treating the area of interest.

Moreover, during the interview, Examiner acquiesced to the fact that in Office Actions for applications drawn to siRNA therapy, USPTO Examining Unit 1635 routinely cites McCaffrey et al., published in July 2002, to support the proposition that the delivery of siRNA to a target location within a patient is unpredictable and has been a problem in the art. Thus, on one hand, the Office asserts that the delivery of the siRNA-based therapies is a problem, and on the other hand, the Examiner in the same Art Unit argues that the instant system for the delivery of siRNA-based therapy during a complex neurosurgical procedure, is obvious.

In fact, the Office has recognized that there is no system which would enable one of skill in the art to deliver the siRNA agent to the target area such as brain. See, for example, selected slides in SPE Schultz's presentation attached hereto as Attachment 5, indicating delivery of siRNA is an unresolved issue. (referring to the 2nd bullet of the 2nd slide, "delivery, delivery, delivery"). Thus, it is the Art Unit's overall position that the state of art teaches away from any motivation to combine the cited references, because delivery has been an unresolved problem.

It is not clear to the Applicant, how the instant Examiner's proposed combination of prior art references overcomes the difficulties associated with delivery of siRNA to such organ as brain. Accordingly, Examiner's combination can not amount to any expectation of success, not with standing, achieving the required targeting precision and avoiding complications related to the brain-blood barrier.

Clearly, these two positions are inconsistent. In view of the admission that the siRNA delivery is a problem, the USPTO first implies that one of ordinary skill in the art

would not think of the instant system. In the course of this Application, the USPTO states that one of ordinary skill in the art would have been motivated to combine the references cited by the Examiner to make the instant system.

At the outset, Applicant states that the Examiner has attempted to meet each element of the instant claims by piecemeal assembly of individual elements described in the prior art. Such piecemeal assembly amounts to no more than an improper hindsight, and therefore this piecemeal assembly of cited references is improper.

Applicant states that the claimed system specifically addresses the long-standing and widely recognized problem of the prior art. The Applicant solved this problem by providing a system which allows for a precise delivery of the siRNA into the targeted location within a patient. Accordingly, the instant claims are allowable even in view of McCaffrey.

EXAMINER IS MISAPPLYING THE OBVIOUSNESS STANDARD

MPEP § 2142 requires that a motivation to combine the references must be present for a *prima facie* case of obviousness. In the instant case, such motivation is lacking. Applicant respectfully reminds the Examiner that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). More importantly, the fact that the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

The most recent Supreme Court Decision in *KSR v. Teleflex* did not abolish the requirement for showing a motivation to combine multiple references. 127 S. Ct. 1727 (2007). Specifically, the Court cautioned against an improper hindsight stating that "patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *Id.* at 1731. The Court further restated that:

> it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known.

Id. Accordingly, the *KSR* decision requires that the Examiner has to show some motivation to combine the references.

None of Xia, Caplen, Whitesell, Davidson, Driscoll, Exhibit A, Clark, Salehi, Matilla, Serra and Morel disclose or suggest the use of any siRNA molecules, let alone the siRNA molecules which can treat spinocerebellar ataxia type 1. Morel and Serra are silent as to the type of intracranial access device best suited for their methodology. There is absolutely no suggestion as to the use of a delivery device that does not interfere with brain imaging during the procedure. Therefore, there is no motivation to combine Serra and Morel with the combination of Xia, Caplen, Whitesell, Davidson, Driscoll, Exhibit A, Clark, Salehi, and Matilla. Applicant also notes that a person of ordinary skill in the art would not think of such a combination due to the delivery associated problems.

Applicant further submits that even if one thought of a combination of Xia, Caplen, Whitesell, Davidson, Driscoll, Exhibit A, Clark, Salehi, Matilla, Serra and Morel, such combination still would not result in all features of claim 1, which specifies that the mapping means must be intra-operative using such catheter that are of material which does not interfere with intra-operative brain imaging.

At least one aspect of the instant invention is to assemble such system wherein each element employed in the instantly claimed system enhances the clinical outcome. The instant claims are directed to systems that employ special intracranial access device, patient specific mapping means and an siRNA agent during brain surgery to enable one of ordinary skill in the art a logarithmically enhanced degree of accuracy when compared to the combined teachings of the cited reference. Essentially, Serra, Morel as well as every other reference relied on by the Examiner disclose or suggest a method and/or a system allowing for only the blind placement of a distal tip of the delivery means (e.g., a catheter), wherein the catheter's path is only theoretically mapped and is not verified during the surgery. Accordingly, assuming that one would have employed all the cited references, there still exist no expectation of success to use the proper delivery port,

proper mapping means, and siRNA, because the teachings of prior art are not complementary to each other.

In order to make a *prima facie* case of obviousness, all limitations of the respective claim should be disclosed or suggested. MPEP § 2142. This burden is not met in the instant case. Therefore, Examiner's application of the obviousness standard is improper.

NOTICE OF ALLOWANCE IS EARNESTLY SOLICITED

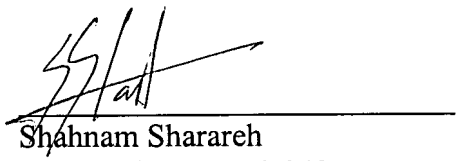
As set forth above, claim 1 is free of art and thus patentable. Claims 10, 14, 24, 25, 86, 87, 89, and 98 depend on claim 1, incorporating all limitations of claim 1. Accordingly, claims 10, 14, 24, 25, 86, 87, 88, and 98 are also allowable.

Claims 90-97 have been added. Even though these claims are directed to another embodiment of the system of the instant invention, they still require that the mapping means should be patient-specific and intra-operative. For the very reasons discussed above, there is no motivation to combine the references used by the Examiner. Further, even if the references are combined, the resulting combination does not disclose or suggest the intra-operative mapping means recited in claim 90. Claims 91-97 depend on claim 90 and incorporating all its limitations. Therefore, claims 90-97 should also be allowable in view of the cited references.

In view of the remarks above, Applicant submits that the pending claims are valid and favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that the Examiner telephone Applicant's attorney at (609) 844-3030 to discuss any additional rejections. The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Date: October 1, 2007

Respectfully submitted,



Shahnam Sharareh
Registration No. 59,040
Attorney for the applicant
Fox Rothschild LLP
Princeton Pike Corporate Center
997 Lenox Drive, Building 3
Lawrenceville, NJ 08648-2311

ATTACHMENT 1

NEW FIGURE 7

ATTACHMENT 2

REPLACEMENT SHEETS FOR PAGES 9, 14, 29-35 OF THE SPECIFICATION AND FIGURE 7

Figure 5 illustrates an investigational device (by Medtronic, Inc. of Minneapolis, MN - schematic of Model 8506), which can be implanted subcutaneously on the cranium, and provides an access port through which therapeutic agents may be delivered to the brain.

Figure 6 illustrates the relation of various neurodegenerative diseases described herein, and the location of treatment with small interfering RNA vectors directed to their intended targeted gene product.

Figure 7 is a schematic side view depiction of a marker tip at the distal end of the catheter used in implementing the method of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention solves two problems in the prior art at the same time: (1) the problem of how to treat neurodegenerative diseases caused by the production in neurons of a protein that has pathogenic properties and (2) the problem of delivery of therapeutic small interfering RNA to affected neurons.

In order to better understand the present invention, a list of terms and the scope of understanding of those terms is provided below.

Terminology

By "alpha-synuclein, BACE1 (including variants thereof, e.g. variants A, B, C, and D), huntingtin, ataxin-1, ataxin-3, and/or atrophin-1 proteins" is meant, a protein or a mutant protein derivative thereof, comprising the amino-acid sequence expressed and/or encoded by alpha-synuclein (Parkinson's disease), and beta-site APP-cleaving enzyme (BACE1 (including variants thereof, e.g. variants A, B, C, and D)) (Alzheimer's disease), huntingtin (Huntington's disease), and ataxin-1 (Spinocerebellar Ataxia Type 1), ataxin-3 (Spinocerebellar Ataxia Type 3 or Machado-Joseph's Disease), and/or dentatorubral-pallidoluysian atrophy (DRPLA) genes and/or the human genomic DNA respectively.

As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism. The cell may be present in an organism which may be a human but is preferably of mammalian origin, e.g., such as humans, cows, sheep, apes, monkeys, swine, dogs, cats, and the like. However, several steps of producing small

By "small interfering RNA" is meant a nucleic acid molecule which has complementarity in a substrate binding region to a specified gene target, and which acts to specifically guide enzymes in the host cell to cleave the target RNA. That is, the small interfering RNA by virtue of the specificity of its sequence and its homology to the RNA target, is able to cause cleavage of the RNA strand and thereby inactivate a target RNA molecule because it is no longer able to be transcribed. These complementary regions allow sufficient hybridization of the small interfering RNA to the target RNA and thus permit cleavage. One hundred percent complementarity often necessary for biological activity and therefore is preferred, but complementarity as low as 90% may also be useful in this invention. The specific small interfering RNA described in the present application are not meant to be limiting and those skilled in the art will recognize that all that is important in a small interfering RNA of this invention is that it have a specific substrate binding site which is complementary to one or more of the target nucleic acid regions.

Small interfering RNAs are double stranded RNA agents that have complementary to (i.e., able to base-pair with) a portion of the target RNA (generally messenger RNA). Generally, such complementarity is 100%, but can be less if desired, such as 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. For example, 19 bases out of 21 bases may be base-paired. In some instances, where selection between various allelic variants is desired, 100% complementary to the target gene is required in order to effectively discern the target sequence from the other allelic sequence. When selecting between allelic targets, choice of length is also an important factor because it is the other factor involved in the percent complementary and the ability to differentiate between allelic differences.

The small interfering RNA sequence needs to be of sufficient length to bring the small interfering RNA and target RNA together through complementary base-pairing interactions. The small interfering RNA of the invention may be of varying lengths. The length of the small interfering RNA is preferably greater than or equal to ten nucleotides and of sufficient length to stably interact with the target RNA; specifically 15-30 nucleotides; more specifically any integer between 15 and 30 nucleotides, such as 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30. By "sufficient length" is meant

these and other devices and systems may be suitable for delivery of small interfering RNA vectors for the treatment of neurodegenerative diseases in accordance with the present invention.

In one preferred embodiment, the method further comprises the steps of implanting a pump outside the brain, the pump coupled to a proximal end of the catheter, and operating the pump to deliver the predetermined dosage of the at least one small interfering RNA or small interfering RNA vector through the discharge portion of the catheter. A further embodiment comprises the further step of periodically refreshing a supply of the at least one small interfering RNA or small interfering RNA vector to the pump outside said brain.

Thus, the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Patent No. 5,735,814 and 6,042,579, and further using a sensor as part of the infusion system to regulate the amount of small interfering RNA vectors delivered to the brain, like that taught in U.S. Patent No. 5,814,014. Other devices and systems can be used in accordance with the method of the present invention, for example, the devices and systems disclosed in U.S. Serial Nos. 09/872,698 (filed June 1, 2001) and 09/864,646 (filed May 23, 2001), which are incorporated herein by reference.

It is preferred to place some means for locating distal end 14 during the access and location process. This is preferably done by applying a marker 46, as shown in FIG. 7, to distal end 14 which is detected during the access and location process. If access and location is accomplished using some form of x-ray radiation, marker 46 is preferably radiopaque. Radiopaque marker 46 renders at least a portion of distal tip 14 opaque to x-rays, enabling the tip to be observed via fluoroscopy or via x-ray during access and location of catheter 10.

In a preferred embodiment, radiopaque marker 46 comprises tantalum powder dispersed in a matrix composed of a biocompatible adhesive, such as those discussed above. Ordinarily, radiopaque marker 46 will be premolded prior to insertion into the lumen 38. After radiopaque marker 46 has been inserted into the lumen 38, a thin coating of the same biocompatible adhesive is preferably applied to the exterior of the hemispherical portion 48. Other materials may also be suitable for radiopaque marker 46,

such as barium or platinum materials.

Alternately, the radiographic marker 46 may be chosen of a material that has sufficient radiodensity for visualization during radiologic procedures, but in powdered form that is dispersed in the catheter tip at the time the catheter tip is molded.

Alternatively, marker 46 may be composed of a material that is compatible to nuclear magnetic resonance imaging (MRI) to enable the tip to be detected during an MRI scan. Preferred material for such a marker 46 is platinum, though barium, tantalum, and similar materials are also suitable. Regardless of whether radiography or MRI is being utilized, the goal of providing a radiographic marker 46 is to enable the operator to accurately detect the precise location of the tip to facilitate placement and later verification of the integrity and position of distal end 14 of catheter 10.

To summarize, the present invention provides methods to deliver small interfering RNA vectors to the human central nervous system, and thus treat neurodegenerative diseases by reducing the production of a pathogenic protein within neurons.

The present invention is directed for use as a treatment for neurodegenerative disorders and/or diseases, comprising Alzheimer's disease, Parkinson's disease, Huntington's disease, Spinocerebellar type 1, type 2, and type 3, and/or any neurodegenerative disease caused or aggravated by the production of a pathogenic protein, or any other neurodegenerative disease caused by the gain of a new, pathogenic function by a mutant protein.

EXAMPLES

Example 1: Construction of a small interfering RNA targeting human ataxin1 mRNA.

As an example of the embodiments of the invention, we have made a small interfering RNA that targets the mRNA for human ataxin1. This small interfering RNA reduces the amount of mRNA for human ataxin1 in human cells, in cell cultures. As a therapy for Spinocerebellar Ataxia Type 1 (SCA1), this same small interfering RNA or a similar small interfering RNA will be delivered to the cells of the cerebellum in the patient's brain, using implanted access ports and catheters. The result will be a reduction

in the amount of ataxin1 protein in these cells, thereby slowing or arresting the progression of the patient's SCA1 disease.

The small interfering RNA against human ataxin1 was been constructed from the nucleotide sequence for human ataxin1. The sequence from human ataxin 1 was retrieved from the publicly-accessible nucleotide database provided by NCBI, retrievable as NCBI accession number NM_000332 (SEQ ID:15). A portion of the human mRNA sequence for ataxin1 was identified as a potential site for small interfering RNA cleavage and also predicted to be single-stranded by MFOLD analysis. In accession NM_000332 (SEQ ID:15), three pairs of anti ataxin1 siRNA targets were constructed:

1. Anti-ataxin1 siRNA targeting the mRNA sequence at sites numbered 945 through 965:

SEQ ID:1 5' - AACCAAGAGCGGAGCAACGAA - 3'
SEQ ID:2 3' - GGTTCTCGCCTCGTTGCTTAA - 5'

2. Anti-ataxin1 siRNA targeting the mRNA sequence at sites numbered 1671 - through 1691:

SEQ ID:3 5' - AACCAAGAGCGGAGCAACGAA - 3'
SEQ ID:4 3' - GGTTCTCGCCTCGTTGCTTAA - 5'

3. Anti-ataxin1 siRNA targeting the mRNA sequence at sites numbered 2750 - through 2770:

SEQ ID:4 5' - AACCAGTACGTCCACATTTCC - 3'
SEQ ID:6 3' - GGTCATGCAGGTGTAAAGGAA - 5'

A series of six deoxyoligonucleotide fragments were designed, ordered and purchased from the MWG Biotech, Inc., custom oligonucleotide synthesis service to provide the six fragments making up the three target sites. Additionally, these oligonucletides were constructed to include an 8 base sequence complementary to the 5' end of the T7 promoter primer included in an siRNA construction kit (Ambion, Inc. catalog number 1620). Each specific oligonucleotide was annealed to the supplied T7

promoter primer, and filled-in with Klenow fragment to generate a full-length DNA template for transcription into RNA. Two in vitro transcribed RNAs (one the antisense to the other) were generated by in vitro transcription reactions then hybridized to each other to make double-stranded RNA. The double-stranded RNA product was treated with DNase (to remove the DNA transcription templates) and RNase (to polish the ends of the double-stranded RNA), and column purified to provide the three siRNAs that were delivered and tested in cells.

Example 2: Delivery of a small interfering RNA targeting human ataxin1 mRNA.

The constructed siRNA molecules 1-3 described in Example 1 were transfected into HEK293 cells. The RNA produced by the transfected cells was harvested and assayed to measure the amount of human ataxin1 mRNA.

Figure 1 shows the results of a quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) assay for the amount of ataxin1 messenger RNA (mRNA) per microgram of total RNA from cultures of HEK 293H cells. Four cell populations were assayed. The first were 293H cells that had been transiently transfected with siRNA against GAPDH, a "housekeeping gene" with no known relationship to ataxin1 mRNA expression. (The siRNA against GAPDH was supplied as a standard control by Ambion, Inc., in their commercially-available kit for making and testing siRNA). The second were 293H cells that had been transiently transfected with siRNA against ataxin1 mRNA at location 1671 in the ataxin1 mRNA sequence. The third were 293H cells transiently transfected with a plasmid containing a ribozyme against ataxin1 mRNA (which cleaves ataxin1 mRNA at position 1364 in the ataxin1 mRNA sequence). The fourth were 293H cells transiently transfected with siRNA against ataxin1 mRNA at location 0945. All cell populations were harvested concurrently for total cellular RNA, at a time point 48 hours after transfection.

On the gels pictured, the amplified DNA products of the RT-PCR reaction were separated by molecular size, using gel electrophoresis, and are visible as bands of varying intensity. Each cell population described was assayed using a series of parallel reactions, shown as a set of lanes at the top or bottom of each gel. Each set of lanes contains two bands per lane. The top band is the DNA product amplified from a known quantity of

DNA added to the reaction to compete with the endogenous cDNA reverse transcribed from the cellular mRNA. If the bands in a given lane are of the same intensity, then the amount of cellular mRNA in the original cell sample can be inferred to be equivalent to the amount of known quantity of DNA added to the reaction tube. From left to right across the lanes, the amount of known DNA standard added was decreased, in the picogram amounts shown. The assay is interpreted by looking for the set of lanes for which the intensity of the bands "crosses over" from being brightest for the DNA standard, to being brightest for the cellular product below it, indicating that the amount of DNA standard is now lower than the amount of cellular mRNA.

On the gel shown in Figure 1, the top set of lanes is from the cells transfected with the ribozyme against ataxin1 mRNA. The comparison of the bands from this cellular sample to the bands from the DNA standards indicates that the amount of ataxin1 mRNA in these cells is between .505 and .303 picograms per microgram of total cellular RNA. The bottom set of lanes is from the cells transfected with siRNA against ataxin1 at position 0945. Analysis of these lanes indicates that the amount of ataxin1 mRNA in these cells is between .303 and .202 picograms per microgram of total cellular RNA.

On the gel shown in Figure 2, the top set of lanes is from the cells transfected with a control siRNA against GAPDH. Analysis of these lanes indicates that the amount of ataxin1 mRNA in these cells is between .711 and .400 picograms per microgram of total cellular RNA. Finally, the bottom set of lanes is from cells transfected with another siRNA against ataxin1, at position 1671. These lanes indicate that the amount of ataxin1 mRNA in these cells is between 0.404 and 0.303 picograms per microgram of total cellular RNA.

In summary, the results of this particular analysis were:

Treatment	Amount of ataxin1 mRNA (picograms per microgram total cellular RNA)		
	Lower bound	Upper bound	Midpoint Estimate
Control (GAPDH)	0.400	0.711	0.555
Ribozyme (A1364A)	0.303	0.505	0.404
siRNA (AT1671)	0.303	0.404	0.353

siRNA (AT0945)	0.202	0.303	0.252

These data indicate that both the AT1671 and AT0945 siRNA against ataxin1 were effective at reducing the amount of ataxin1 mRNA in these cells within 48 hours after transfection, and that the siRNA were more effective at the reduction of ataxin1 mRNA than was this anti-ataxin1 ribozyme.

It should be noted that the exemplified method for constructing the small interfering RNA to be used as the therapeutic agents in the invention (that is, assembly from oligonucleotides using in vitro transcription and hybridization) is only one possible means for making the therapeutic small interfering RNA. Other larger scale, more efficient methods for manufacturing small interfering RNA may be used to produce the clinical grade and clinical quantities used for treating human patients, without altering the essence of the invention or departing from the spirit and scope of this invention, as set forth in the appended claims.

Example 3: Allele-Specific Reduction of Ataxin1 Expression Using Small, Interfering RNA

In heterozygous patients, if a single nucleotide polymorphism (SNP) were to differ between the mutant and normal length allele, an appropriate siRNA might selectively reduce expression of only the mutant allele. We have tested 293, DAOY, SK-N-SH, and HeLa cells using allele-specific RT-PCR for a SNP at position +927 downstream form the SCA1 start codon (see Accession NT_007592). HeLa cells express a 927C but no 927T allele, while 293 cells express a 927T but no 927C allele. DAOY and SK-N-SH cells express both allelic variants. We have created allele-specific siRNA centered at this site. Results of assays for allele-specific suppression of endogenous SCA1 mRNA by these siRNA variants will be presented.

Example 4 : Construction of Small, Interfering RNA Viral Vectors

A selectable reporter plasmid, pAAV-U6-Tracer is constructed for cloning siRNA. (See Figure 3). The plasmid pAAV-U6-Tracer was constructed to contain the inverted terminal repeats (ITR) of adeno-associated virus, flanking the U6 RNA

polymerase III promoter from pSilencer (Ambion), and the EF1a promoter, green fluorescence protein, Zeocin^r resistance, and SV40 poly A from pTracer (Invitrogen). The gene segments are cloned as shown in Figure 3. Oligonucleotides for expressing siRNA are cloned into the multiple cloning region just downstream in the 3' direction from the U6 RNA polymerase III promoter.

HEK293 Cells are cotransfected with pAAV-siRNA, pHelper, and pAAV-RC to make viral producer cells, where the pAAV-RC and pHelper plasmids are part of the three plasmid AAV production system Avigen, Inc.) . The producer 293 cells are grown in culture are used to isolate recombinant viruses, which is used to transfect secondary cells: HeLa Cells, DAOY cells, and SK-N-SH cells.

ATTACHMENT 3

MARKED UP SHEETS INDICATING THE AMENDMENTS TO PAGES 9, 14, 29-30 OF THE SPECIFICATION

(Please note that replacement sheets 31-35 contain the same text as the original pages 30-34. However, due to the material incorporated into page 29, the pages have been renumbered.)

Figure 5 illustrates an investigational device (by Medtronic, Inc. of Minneapolis, MN - schematic of Model 8506), which can be implanted subcutaneously on the cranium, and provides an access port through which therapeutic agents may be delivered to the brain.

Figure 6 illustrates the relation of various neurodegenerative diseases described herein, and the location of treatment with small interfering RNA vectors directed to their intended targeted gene product.

Figure 7 is a schematic side view depiction of a marker tip at the distal end of the catheter used in implementing the method of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention solves two problems in the prior art at the same time: (1) the problem of how to treat neurodegenerative diseases caused by the production in neurons of a protein that has pathogenic properties and (2) the problem of delivery of therapeutic small interfering RNA to affected neurons.

In order to better understand the present invention, a list of terms and the scope of understanding of those terms is provided below.

Terminology

By "alpha-synuclein, BACE1 (including variants thereof, e.g. variants A, B, C, and D), huntingtin, ataxin-1, ataxin-3, and/or atrophin-1 proteins" is meant, a protein or a mutant protein derivative thereof, comprising the amino-acid sequence expressed and/or encoded by alpha-synuclein (Parkinson's disease), and beta-site APP-cleaving enzyme (BACE1 (including variants thereof, e.g. variants A, B, C, and D)) (Alzheimer's disease), huntingtin (Huntington's disease), and ataxin-1 (Spinocerebellar Ataxia Type 1), ataxin-3 (Spinocerebellar Ataxia Type 3 or Machado-Joseph's Disease), and/or dentatorubral-pallidoluysian atrophy (DRPLA) genes and/or the human genomic DNA respectively.

As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism. The cell may be present in an organism which may be a human but is preferably of mammalian origin, e.g., such as humans, cows, sheep, apes, monkeys, swine, dogs, cats, and the like. However, several steps of producing small

By "small interfering RNA" is meant a nucleic acid molecule which has complementarity in a substrate binding region to a specified gene target, and which acts to specifically guide enzymes in the host cell to cleave the target RNA. That is, the small interfering RNA by virtue of the specificity of its sequence and its homology to the RNA target, is able to cause cleavage of the RNA strand and thereby inactivate a target RNA molecule because it is no longer able to be transcribed. These complementary regions allow sufficient hybridization of the small interfering RNA to the target RNA and thus permit cleavage. One hundred percent complementarity often necessary for biological activity and therefore is preferred, but complementarity as low as 90% may also be useful in this invention. The specific small interfering RNA described in the present application are not meant to be limiting and those skilled in the art will recognize that all that is important in a small interfering RNA of this invention is that it have a specific substrate binding site which is complementary to one or more of the target nucleic acid regions.

Small interfering RNAs are double stranded RNA agents that have complementary to (i.e., able to base-pair with) a portion of the target RNA (generally messenger RNA). Generally, such complementarity is 100%, but can be less if desired, such as 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. For example, 19 bases out of 21 bases may be base-paired. In some instances, where selection between various allelic variants is desired, 100% complementary to the target gene is required in order to effectively discern the target sequence from the other allelic sequence. When selecting between allelic targets, choice of length is also an important factor because it is the other factor involved in the percent complementary and the ability to differentiate between allelic differences.

~~XXXX~~

The small interfering RNA sequence needs to be of sufficient length to bring the small interfering RNA and target RNA together through complementary base-pairing interactions. The small interfering RNA of the invention may be of varying lengths. The length of the small interfering RNA is preferably greater than or equal to ten nucleotides and of sufficient length to stably interact with the target RNA; specifically 15-30 nucleotides; more specifically any integer between 15 and 30 nucleotides, such as 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30. By "sufficient length" is meant

these and other devices and systems may be suitable for delivery of small interfering RNA vectors for the treatment of neurodegenerative diseases in accordance with the present invention.

In one preferred embodiment, the method further comprises the steps of implanting a pump outside the brain, the pump coupled to a proximal end of the catheter, and operating the pump to deliver the predetermined dosage of the at least one small interfering RNA or small interfering RNA vector through the discharge portion of the catheter. A further embodiment comprises the further step of periodically refreshing a supply of the at least one small interfering RNA or small interfering RNA vector to the pump outside said brain.

Thus, the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Patent No. 5,735,814 and 6,042,579, and further using a sensor as part of the infusion system to regulate the amount of small interfering RNA vectors delivered to the brain, like that taught in U.S. Patent No. 5,814,014. Other devices and systems can be used in accordance with the method of the present invention, for example, the devices and systems disclosed in U.S. Serial Nos. 09/872,698 (filed June 1, 2001) and 09/864,646 (filed May 23, 2001), which are incorporated herein by reference.

It is preferred to place some means for locating distal end 14 during the access and location process. This is preferably done by applying a marker 46, as shown in FIG. 7, to distal end 14 which is detected during the access and location process. If access and location is accomplished using some form of x-ray radiation, marker 46 is preferably radiopaque. Radiopaque marker 46 renders at least a portion of distal tip 14 opaque to x-rays, enabling the tip to be observed via fluoroscopy or via x-ray during access and location of catheter 10.

In a preferred embodiment, radiopaque marker 46 comprises tantalum powder dispersed in a matrix composed of a biocompatible adhesive, such as those discussed above. Ordinarily, radiopaque marker 46 will be premolded prior to insertion into the lumen 38. After radiopaque marker 46 has been inserted into the lumen 38, a thin coating of the same biocompatible adhesive is preferably applied to the exterior of the hemispherical portion 48. Other materials may also be suitable for radiopaque marker 46,

such as barium or platinum materials.

Alternately, the radiographic marker 46 may be chosen of a material that has sufficient radiodensity for visualization during radiologic procedures, but in powdered form that is dispersed in the catheter tip at the time the catheter tip is molded.

Alternatively, marker 46 may be composed of a material that is compatible to nuclear magnetic resonance imaging (MRI) to enable the tip to be detected during an MRI scan. Preferred material for such a marker 46 is platinum, though barium, tantalum, and similar materials are also suitable. Regardless of whether radiography or MRI is being utilized, the goal of providing a radiographic marker 46 is to enable the operator to accurately detect the precise location of the tip to facilitate placement and later verification of the integrity and position of distal end 14 of catheter 10.

To summarize, the present invention provides methods to deliver small interfering RNA vectors to the human central nervous system, and thus treat neurodegenerative diseases by reducing the production of a pathogenic protein within neurons.

The present invention is directed for use as a treatment for neurodegenerative disorders and/or diseases, comprising Alzheimer's disease, Parkinson's disease, Huntington's disease, Spinocerebellar type l, type 2, and type 3, and/or any neurodegenerative disease caused or aggravated by the production of a pathogenic protein, or any other neurodegenerative disease caused by the gain of a new, pathogenic function by a mutant protein.

ATTACHMENT 4

COPY OF APPLICATION SN 09/872,698
AS FILED

PATENT
ATTORNEY DOCKET: P-3226

APPLICATION FOR UNITED STATES LETTERS PATENT

for

THERAPEUTIC METHOD FOR TREATMENT OF ALZHEIMER'S DISEASE

by

DENNIS D. ELSBERRY, D.V.M.

ATTORNEY OF RECORD:

Curtis D. Kinghorn
MEDTRONIC, INC.
7000 Central Avenue NE
Minneapolis, MN 55432
Telephone: 612-574-3346
Facsimile: 612-574-3233

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Printed Name: MARY ANN GLYNN

Background of the Invention

Field of the Invention

This invention relates to a method of treating Alzheimer's disease and more specifically relates to delivering therapeutic nonsteroidal anti-inflammatory agents directly into the central nervous system or specific brain structures.

Description of the Related Art

Studies support an inverse relationship between anti-inflammatory medications used for treating patients with rheumatoid arthritis and an associated low prevalence of Alzheimer's disease [J.B. Rich et.al., *Neurology* 45:51-55, 1995]. Controlled studies of twin pairs having Alzheimer's disease onset greater than 3 years provide additional support that prior treatment with anti-inflammatory medications serves a protective role in Alzheimer's disease. [J.C.S. Breitner, et.,al., *Neurology* 44:227-232, 1994] Specifically, controlled double-blinded studies have found that the anti-inflammatory agent "indomethacin" administered orally has a therapeutic benefit for mild to moderately cognitively impaired Alzheimer's disease patients, and treatment with indomethacin during early stages of the disease has a retarding affect on disease progression compared to the placebo treated control group. [J. Rogers, et.al., *Neurology* 43:1609-1612, 1993] Alzheimer's patients with moderate cognitive impairment treated with indomethacin also exhibit a reduction in cognitive decline. However, patients treated with oral indomethacin developed drug related adverse effects that required their treatment to be discontinued and their removal from the study.

Studies have shown indomethacin works at the cellular areas of the brain affected by Alzheimer's disease. These cellular areas include the hippocampus, entorhinal cortex, basal forebrain, amygdala and nucleus basalis of Meynert. In the normal brain, various enzyme systems act on amyloid precursor proteins to form peptides required for physiological brain functions including cellular membrane repair.

An example of normal amyloid protein processing is the action of an endoprotease termed "alpha-secretase." Alpha-secretase cleaves the amyloid precursor protein resulting in non-amyloidogenic peptide fragments. These non-amyloidogenic peptide

fragments are required for normal cellular function (S.B. Roberts et.al., *Journal of Biological Chemistry* 269:3111-3116, 1994).

Other endoproteases, termed "beta-" and "gamma-secretases", cleave the amyloid precursor protein to form amyloidogenic fragments capable of interacting with several other cellular proteins. The interaction of the amyloidogenic fragments and other cellular proteins forms enzymes that become the foci of neurotoxicity and subsequently neuritic plaques (P. Eikelenboom, et.al., *TiPS* 15:447-450, 1994). In particular, beta-secretase cleaves the amyloid precursor protein to form fragments that result in increased calcium influx into the affected neurons. This increased calcium influx affects the intracellular pH and cytokine induction of the neurons which triggers intracellular enzymatic activation including lipoxygenase and cyclooxygenase up-regulation.

These enzymes resulting from the interaction of the amyloidogenic fragments and other cellular proteins further disrupt intracellular microtubule metabolism with inhibition of protein transport blocking neurotransmission along the neurite's axon. The result of this process is senile neuritic plaque formation and neurofibrillary tangles associated with Alzheimer's disease.

Although the specific causes for increased cellular production of altered secretase activity in specific brain regions is not well understood, it is known that this dysfunctional enzymatic activity results in progressive dendritic pruning, neuronal loss and damage with marked cognitive decrements over time.

A problem with orally administered indomethacin or other nonsteroidal anti-inflammatory drugs is unpleasant side effects including severe nausea and gastric ulcers which patients develop following chronic use. Further, with chronic oral therapy the therapeutic value diminishes over time requiring dose escalation. In addition, limited transport of indomethacin or other nonsteroidal anti-inflammatory drugs across the blood brain barrier increases the potential for systemic adverse side-effects.

In order to maintain the same therapeutic affect with disease progression, the dose of indomethacin taken orally must increase. In patients having adverse side-effects, treatment escalation is not possible. Thus, oral administration of drugs such as indomethacin is inherently dose-limiting.

In addition to the problems just mentioned with orally administered indomethacin or similar nonsteroidal anti-inflammatory drugs, the amount of drug entering the patient's blood system is minimized by uptake of the drugs by the gastrointestinal system.

It is therefore desirable to produce a chronic treatment regimen allowing the direct delivery of indomethacin or similar nonsteroidal anti-inflammatory drugs, having therapeutic value against the affect of amyloidogenic protein neurotoxicity, to the desired area of the brain. Such a treatment regimen is necessary to by-pass the adverse side-effects produced by orally administered drug and subsequent drug receptor uptake by the gastrointestinal system.

Summary of the Invention

A method of treatment for Alzheimer's disease is disclosed. The method comprises delivering indomethacin or similar nonsteroidal anti-inflammatory drugs through an implanted catheter positioned directly into the hippocampus with a delivery catheter attached to a drug delivery pump containing the therapeutic drug. The catheter has a flexible distal end that is implanted directly in the hippocampus. Alternatively, the distal end of the catheter may be positioned within the lateral ventricles of the cerebroventricular system which communicates anatomically via the inferior horn of the lateral ventricle immediately adjacent to the hippocampus.

The distal end has either a porous tip or a closed end. Where the distal end is closed, or a plurality of elution holes are present. Indomethacin or a similar drug is delivered to the hippocampus directly or indirectly via the cerebroventricular system. A pump is coupled to the catheter for delivery of the drug at a selected infusion rate. The combination of a catheter implanted directly in the brain and a pump to pump the drug through the catheter and out the distal end of the catheter into the brain allows direct access across the blood brain barrier. Thus, less drug is required for the desired therapeutic affect compared to oral or systemic delivery since drug is targeted within the central nervous system. Further, drug delivery directly to the brain limits drug access into the systemic circulation preventing access to secondary therapeutic targets associated with adverse side-effects associated with oral or systemic drug delivery.

The catheter preferably comprises a first tubular portion that has a generally cylindrical lumen of a first internal diameter and is composed of a relatively impermeable flexible material. A second tubular portion has an open end disposed within the lumen and a closed distal end disposed without the lumen. The second tubular portion is composed of a flexible, porous material having a preselected microporosity that is operable to permit the therapeutic drug, for example indomethacin, to flow from the catheter into the hippocampus. The second tubular portion is selectively moveable with respect to the first tubular portion.

Alternatively, a catheter for delivering indomethacin or a similar drug to a selected site within the hippocampus comprises a tubular portion composed of a relatively impermeable material. The distal end of the tubular portion is closed and has one or more elution holes through which indomethacin contained within the tubular portion exits the catheter.

It is therefore an object of the invention to provide a method and device for treating Alzheimer's disease.

It is another object of the invention to administer indomethacin or another similar drug more effectively to the brain.

It is another object of the invention to administer indomethacin or another similar drug directly to the area of interest in the brain.

It is another object of the invention to administer indomethacin or another similar drug in tightly controlled amounts to the brain.

It is another object of the invention to administer indomethacin or another similar drug in minute dosages over time to the brain.

It is another object of the invention to continuously administer indomethacin or another similar drug over time to the brain.

It is another object of the invention to administer indomethacin or another similar drug over time to the hippocampus in the brain.

It is another object of the invention to administer indomethacin or another similar drug over time to the lateral ventricles in the brain.

It is another object of the invention to administer indomethacin or another similar drug over time to the marginal aspects of the lateral ventricles in the brain.

It is another object of the invention to administer indomethacin or another similar drug to the brain directly across the blood brain barrier

These objects and advantages of the invention, as well as others that will be clear to those skilled in the art, will become apparent upon reading the following detailed description and references to the drawings. In the drawings and throughout this disclosure, like elements wherever referred to, are referenced with like reference numbers.

Brief Description of the Drawings

FIG. 1 is a saggital view of a human brain with a catheter placed so that the distal end of the catheter is positioned in the hippocampus.

FIG. 2A is a transverse view of the human brain with the relationship of the hippocampus with respect to the lateral ventricle.

FIG. 2B is a coronal view of the relationship of the hippocampus with respect to the inferior horn of the lateral ventricle.

FIG. 3 is a schematic depiction of the preferred embodiment of a means for implementing the invention with direct access into the hippocampus.

FIG. 3A is a schematic depiction of an alternate embodiment of a means for implementing the invention with direct access into the hippocampus.

FIG. 4 is a schematic depiction of an alternate embodiment of a means for implementing the invention with direct access into the lateral ventricle.

FIG. 4A is a schematic depiction of an alternate embodiment of a means for implementing the invention with direct access into the lateral ventricle.

FIG. 5 is a schematic side view depiction of a preferred embodiment of a catheter attached to an infusion pump used in implementing the method of the invention.

FIG. 6 is a schematic side view depiction of an alternate embodiment of catheter attached to an infusion pump used in implementing the method of the invention.

FIG. 7 is a schematic side view depiction of a marker tip used with the catheters of FIGS. 5 and 6.

FIG. 8 is a schematic side view depiction of a method of placing a catheter into the hippocampus.

FIG. 9 is a schematic side view depiction of a method of placing a catheter into the lateral ventricle.

Description of the Preferred Embodiments

In the invention, indomethacin or a similar drug is delivered directly into a patient's hippocampus 18. Throughout this disclosure, reference to indomethacin includes reference to drugs similar to indomethacin. Some of these drugs include therapeutic nonsteroidal anti-inflammatory agents such as lipoxygenase or cyclooxygenase inhibitors. Such nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action may include: acetaminophen, ibuprofen, fenoprofen, flurbiprofen, ketoprofen, naproxen, piroxicam, zomepirac, diclofenace, and sulindac, whereas nordihydroguaiaretic acid is a potent inhibitor of 5-lipoxygenase. Also throughout this disclosure, unless stated otherwise, reference to a patient's hippocampus 18 also refers to a patient's lateral ventricle which lies immediately adjacent to the hippocampus 18.

As shown in FIG. 1, this is accomplished by implanting a catheter 10 having a proximal end 12 and a distal end 14 in a patient's brain 16 so that distal end 14 is located in the patient's hippocampus 18. FIGS. 2A and 2B are transverse and coronal views of the human brain 16 illustrating the relationship of the hippocampus 18 to the lateral ventricle 11.

In the invention, proximal end 12 is attached to a source of indomethacin. This is preferably accomplished by attaching proximal end 12 to an implantable infusion pump ("IIP") 20 through a connecting catheter 22 having a proximal end 24 and distal end 26. Distal end 26 is attached to IIP 20 as shown in FIG. 3. Alternately, proximal end 12 may be attached to a source of indomethacin by being connected via an implanted access port ("CAP") 27 for percutaneous access to an external infusion pump 28 as shown in FIG. 3A. The combination of IIP 20 with catheter 10 is preferred because, as will be explained hereafter, it is believed to be more safe for continuously infusing indomethacin to the

hippocampus 18 to obtain the maximum therapeutic effect. Use of IIP 20 allows indomethacin to be administered in tightly controlled, yet minute dosages over time.

In the invention alternately, indomethacin is delivered directly to a patient's lateral ventricle 11. As shown in FIG. 4, this is accomplished by implanting a catheter 10 having a proximal end 12 and a distal end 14 in a patient's brain so that the distal end 14 is located in the patient's lateral ventricle 11.

In the invention, proximal end 12 is attached to a source of indomethacin. This is preferably accomplished by attaching proximal end 12 to an IIP 20 through a connecting catheter 22 having a proximal end 24 and a distal end 26. Distal end 26 is attached to proximal end 12 while proximal end 24 is attached to IIP 20. Alternately, proximal end 12 may by attached to a source of indomethacin by being connected to an external infusion pump 28 as shown in FIG. 4A. The combination of IIP 20 with catheter 10 is preferred to continuously infuse indomethacin to the lateral ventricle 11. The alternate infusion of indomethacin to the lateral ventricle 11 allows for safe access for perfusing the marginal aspect of hippocampus 18.

The detailed structure of a preferred embodiment of catheter 10 is shown in FIG. 5. Catheter 10 and distal end 14 are shown in an enlarged cross sectional view. The size of catheter 10 is not shown for simplicity of illustration.

As has been mentioned, proximal end 12 is preferable coupled to distal end 26 of connecting catheter 22 and the proximal end 24 of connecting catheter 22 is attached to IIP 20. The connection between proximal end 12 and distal end 26 and the connection between proximal end 24 and IIP 20 is shown schematically in FIG. 5. It should be understood that the actual types of connection will vary depending upon the particular type of connecting catheter 22 and IIP 20 or CAP used as will be well understood by those skilled in the art.

Catheter 10 preferably comprises an elongated tubular portion 30 having a central lumen 32. Catheter 10 terminates at the most distal end of distal end 14 in tip 34. Tubular portion 30 preferably composed of a material that will expand in response to an external stimulus such as heat or a chemical solvent.

In one preferred embodiment, the tubular portion 30 is composed of a relatively impermeable material such as polyacrylonitrile. Polyacrylonitrile will expand in response to an external stimuli such as heat, and will return to its original shape upon cooling.

In an alternate preferred embodiment, tubular portion 30 is composed of enhanced tear resistant silicone elastomer or polyurethane, which, when exposed to an external stimulus such as a chemical solvent like freon, will expand. When the solvent evaporates, the silicone elastomer or polyurethane will return to its original shape.

Whether a heat sensitive or solvent sensitive material is used, the tubular portion 30 should be biocompatible and sufficiently flexible to facilitate insertion. A durometer shore value of 80A is preferred. Tip 34 is preferably rounded to minimize tissue disruption during insertion and location of distal end 14 as will be described hereafter. Tubular portion 30 preferably has an externally tapered distal end surface 36 to minimize tissue disruption during insertion.

Catheter tip 34 has a generally tubular shape and is designed to fit snugly within lumen 32. Catheter tip 34 has a lumen 38 to receive indomethacin from lumen 32. Lumen 32 and the external diameter of catheter tip 34 should be sized so that there is a zero tolerance therebetween. A snug fit is desirable to maintain the position of catheter tip 34 in relation to tubular portion 30 and to discourage seepage of indomethacin between the interface of the exterior of catheter tip 34 and the interior surface of tubular portion 30. However, as discussed more fully below, under certain conditions, catheter 10 may be customized by moving catheter tip 34 in relation to tubular portion 30.

Catheter tip 34 is preferable composed of a porous material such as polysulfone hollow fiber, manufactured by Amicon, although polyethylene, polyamides, polypropylene and expanded polytetrafluoroethylene (ePTFE) are also suitable. Catheter tip 34 is preferable porous along its entire length to enable indomethacin to flow into the hippocampus 18. The preferred pore size is approximately ranged between 0.1-0.2 microns.

It is preferred that the maximum pore size be less than or equal to approximately 0.2 microns to prevent any bacterial agent that may be present inside catheter 10 from entering into the hippocampus 18 or lateral ventricle 11. Furthermore, at larger pore

sizes, there is the potential for tissue in-growth that may restrict the flow of indomethacin out of catheter tip 34. By making the entire length of catheter tip 34 porous, a more uniform volume distribution of indomethacin is provided. Unlike a catheter tip that has a single elution hole or a few elution holes, catheter tip 34 in this embodiment dispenses indomethacin in a nearly 360 degree pattern along the entire length of catheter tip 34 that is exposed to the hippocampus 18 or lateral ventricle 11.

Although the preferred embodiment of catheter tip 34 is a porous tip along its entire length, it is also possible to have a catheter tip 34 that has a single elution hole or a few elution holes along its length. Throughout this disclosure, the length of the portion of catheter tip 34 that is exposed to the hippocampus 18 or lateral ventricle 11, whether catheter tip 34 is continuously porous or has one or a few elution holes, is represented by "x."

As described above, tubular portion 30 is composed of a material that will expand in response to an external stimulus such as hear or a chemical solvent. As a result, length x may be custom selected by the physician at the time of insertion. When tubular portion 30 expands in response to the external stimulus, the snug fit between catheter tip 34 and tubular portion 30 is relieved, and the physician may slide catheter tip 34 with respect to tubular portion 30 by hand to achieve the desired length x. The material from which tubular portion 30 is composed, is selected so that when the external stimulus is removed, tubular portion 30 returns to its ordinary shape, thereby reestablishing the near zero tolerance fit between tubular portion 30 and catheter tip 34.

Alternately, length x may be set at the time of manufacture. Catheters 10 may be manufactured having a variety of lengths x for the portion of catheter tip 34 that will be exposed to the hippocampus 18 or lateral ventricle 11. Lengths x are preselected to produce catheters 10 for predetermined applications in the hippocampus 18 or lateral ventricle 11. These applications may be determined by the specific location in the hippocampus 18 where distal end 14 will be located and the size of the hippocampus 18 of a particular patient. Once the length x has been determined for a catheter 10, the length x may be established on catheter tip 34 and catheter tip 34 may be attached to tubular portion 30 as described above.

In an alternate design for catheter 10, chosen in FIG. 6, distal end 14 is closed. One or a plurality of elution holes 40 extent through distal end 14 so that the indomethacin flowing through catheter 10 may exit catheter 10 through elution holes 40. In this embodiment, the entire catheter 10 is preferably made of a relatively impermeable material such as polyacrylonitrile, polyethylene, polypropylene, or silicone elastomer.

In any of the embodiments for catheter 10, distal end 14 must be sufficiently pliable so that it may move to conform to the structure of the brain in the hippocampus 18 or lateral ventricle 11 as catheter 10 is implanted in the patient as will be described hereafter. This compliance may be accomplished by polymer compositions of low durometer materials.

To practice the invention, distal end 14 is surgically implanted in the brain 16 with distal end 14 specifically located in the patient's hippocampus 18 or lateral ventricle 11. This is preferably done by accessing the hippocampus 18 through a posterior occipital lobe. This produces the least damage to the patient's motor cortex. Similarly, accessing the lateral ventricle 11 may be performed anteriorally through the frontal lobe or posteriorally through the occipital lobe to prevent damaging the motor cortex and affecting the patient's motor function. Typically a trocar 42 or catheter 10 containing a stylet 44 is introduced through the selected lobe to the patient's hippocampus 18 or lateral ventricle 11. Access and location of the trocar 42 or catheter 10 containing a stylet 44 is preferably done using well known external triangulation techniques, stereotactic placement techniques, or magnetic resonance imaging (MRI) techniques such as are commonly used, among other things, in the placement of hydrocephalic shunts.

As shown in FIG. 8, where a trocar 42 is used to access the hippocampus 18, once the trocar 42 is located in the hippocampus 18, catheter 10 is passed through the trocar 42 so that distal end 14 leaves the trocar 42 and enters the hippocampus 18. Once distal end 14 is free of the trocar 42, because distal end 14 is pliable, distal end 14 will move to accommodate the structure of the hippocampus 18. After distal end 14 is located in the hippocampus 18, the trocar 42 is removed. Proximal end 12 is attached to a source of indomethacin.

As shown in FIG. 9 where catheter 10 is located in the hippocampus 18 using a stylet 44, a stylet 44 is placed in lumen 32 to add rigidity to catheter 10. Distal end 14 is then moved to the desired location in the hippocampus 18 or lateral ventricle 11. When distal end 14 is determined to be at the desired location in the hippocampus 18 or lateral ventricle 11, the stylet is removed. When the stylet 44 is removed, because distal end 14 is pliable, distal end 14 will adapt itself to the internal structure of either the hippocampus 18 or lateral ventricle 11. After the stylet 44 is removed, proximal end 12 is attached to a source of indomethacin.

It is preferred to place some means for locating distal end 14 during the access and location process. This is preferably done by applying a marker 46, as shown in FIG. 7, to distal end 14 is detected during the access and location process. If access and location is accomplished using some form of x-ray radiation, marker 46 is preferably radiopaque. Radiopaque marker 46 renders at least a portion of distal tip 14 opaque to x-rays, enabling the tip 34 to be observed via fluoroscopy or via x-ray during access and location of catheter 10.

In a preferred embodiment, the marker 46 comprises a semispherical portion 48 that has a cylindrical nipple 50 emanating away therefrom. Hemispherical portion 48 provides a rounded profile for minimizing tissue disruption during insertion. Cylindrical nipple 50 is sized to fit snugly within the lumen 38 and is held in place via a suitable biocompatible adhesive, such as a biocompatible medical silicone adhesive or a medical urethane adhesive..

In a preferred embodiment, radiopaque marker 46 comprises tantalum powder dispersed in a matrix composed of a biocompatible adhesive, such as those discussed above. The preferred ratio of tantalum to adhesive is 3 to 2. Ordinarily, radiopaque marker 46 will be premolded prior to insertion into the lumen 38. After radiopaque marker 46 has been inserted into the lumen 38, a thin coating of the same biocompatible adhesive is preferably applied to the exterior of the hemispherical portion 48. Other materials may also be suitable for radiopaque marker 46, such as barium or platinum materials.

Alternately, the radiographic marker 46 may be chosen of a material that has sufficient radiodensity for visualization during radiologic procedures, but in powdered form that is dispersed in the catheter tip 34 at the time the catheter tip 34 is molded.

Alternatively, marker 46 may be composed of a material that is compatible to nuclear magnetic resonance imaging (MRI) to enable the tip 34 to be detected during a MRI scan. Preferred material for such a marker 46 is platinum, though barium, tantalum, and similar materials are also suitable. Regardless of whether radiography or MRI is being utilized, the goal of providing a radiographic marker 46 is to enable the operator to accurately detect the precise location of the tip 34 to facilitate placement and later verification of the integrity and position of distal end 14 of catheter 10.

After distal end 14 has been located in the hippocampus 18, proximal end 12 of catheter 10 is attached to a source of indomethacin. Where the source of indomethacin is IIP 20, proximal end 12 is attached to distal end 26 of connecting catheter 22. Connecting catheter 22 is subsequently tunneled subcutaneously under the scalp, behind the ear and to a pectoral or abdominal site where IIP 20 will be implanted. IIP 20 may be any of a number of commercially available implantable infusion pumps such as, for example, the SynchroMed® pump, Model 8611H, manufactured by Medtronic, Inc., Minneapolis, MN.

Alternately, after distal end 14 has been located in the hippocampus 18 or lateral ventricle 11, proximal end 12 of catheter 10 may be attached to an external source of indomethacin. In this case, proximal end 12 is attached to an access port 52 placed in the patient's skull. Access port 52 is in turn connected to a connecting catheter 54 that is attached to an external pump 28 that is connected to a reservoir of indomethacin (not shown). Pump 28 may be any of a number of commercially available external infusion pumps such as, for example, Pharmacia Deltec, Inc. ambulatory infusion pumps.

Once distal end 14 has been located in the hippocampus 18 or lateral ventricle 11 and proximal end 12 has been attached to either IIP 20 or an external pump 28, indomethacin is infused through catheter 10 to exit catheter 10 distal end 14. In the embodiment of catheter 10 having a porous distal end 24, indomethacin exits catheter 10 through the porous material. In the embodiment of catheter 10 having a closed distal end

14, indomethacin exits catheter 10 through elution holes 40. In either embodiment for distal end 14, the following are believed to be desirable dosages and flow rates for the introduction of indomethacin into the hippocampus 18 ranging from 0.1 -1.0 microliters per hour.

It is believed that the disclosed invention will have particular therapeutic value if indomethacin is continually infused to the patient's hippocampus 18. Therefore, in selecting the material for catheter 10, care should be taken to ensure that the materials chosen is compatible with long term exposure to indomethacin.

By practicing the disclosed invention, the unpleasant side effects associated with orally administering indomethacin or similar drugs are eliminated. In addition, higher concentrations of indomethacin may be presented to the hippocampus 18 or the lateral ventricles of the cerebroventricular system than is possible with orally administered indomethacin.

Many modifications and variations may be made in the techniques and structures described and illustrated herein without departing from the spirit and scope of the present invention. For example, the system could be used to infuse a cytostatic agent into a malignant mass located in the variety of places in the body or infuse a nerve growth factor into the intrathecal space of the spinal column. Accordingly, the techniques and structures described and illustrated here in should be understood to be illustrative only and not limiting upon the scope of the present invention.

Claims

What is claimed is:

1. A catheter system for delivering indomethacin to a selected site within a hippocampus or lateral ventricle, comprising:

a pump;

a source of indomethacin in fluid communication with the pump; and

a catheter coupled to the pump, the catheter having a distal and a proximal end, the catheter having a first tubular portion and a second tubular portion, the first tubular portion being made from a relatively impermeable material and having a first tubular portion lumen, the first tubular portion having a proximal and a distal end, the second tubular portion having a second tubular portion lumen and an open end and a closed end, the open end disposed within the first tubular portion lumen at the distal end of the first tubular portion, the second tubular portion having a closed end disposed distally of the distal end of the first tubular portion, the second tubular portion being made of a porous material having a preselected microporosity that permits indomethacin to flow through the second tubular portion lumen and out of the catheter through the second tubular portion into the hippocampus or lateral ventricle.

2. The system of claim 1 wherein the second tubular portion is selectively moveable with respect to the first tubular portion.

3. The system of claim 1 wherein the pump is adapted for subcutaneous placement.

4. The system of claim 1 wherein the porous material of the second tubular portion has a microporosity of less than or equal to 0.22 microns.

5. The system of claim 4 wherein the porous material of the second tubular portion is selected from the group of materials consisting of polyamide, polyethylene, polypropylene and hollow fiber polysulfone.

6. The system of claim 1 wherein the impermeable material of the first tubular portion is selected from the group of materials consisting of polyurethane, silicone and polyacrylonitrile.

7. The system of claim 1 wherein the impermeable material of the first tubular portion expands when exposed to a preselected solvent so that the internal diameter of the first tubular portion increases from a first internal diameter to a second internal diameter whereby the second tubular portion may be moved relative to the first tubular portion after the first tubular portion has been exposed to the preselected solvent and wherein the first tubular portion contracts when the solvent is removed from contact with the first tubular portion so that the first tubular portion returns to the first internal diameter.

8. The system of claim 1 wherein the impermeable material of the first tubular portion expands when heated so that the internal diameter of the first tubular portion increases from a first internal diameter to a second internal diameter whereby the second tubular portion may be moved relative to the first tubular portion after the first tubular portion has been exposed to heat and wherein the first tubular portion contracts when the first tubular portion is removed from contact with heat so that the first tubular portion returns to the first internal diameter.

9. The system of claim 1 wherein a portion of the distal end of the second tubular portion contains a radiographic marker.

10. The system of claim 1 wherein a portion of the distal end of the second tubular portion contains a nuclear magnetic resonance marker.

11. A catheter system for delivering a nonsteroidal anti-inflammatory agent having cyclooxygenase inhibitor action to a selected site within a hippocampus or lateral ventricle, comprising:

a pump;

a source of nonsteroidal anti-inflammatory agent having cyclooxygenase inhibitor action in fluid communication with the pump; and

a catheter coupled to the pump, the catheter having a distal and a proximal end, the catheter having a first tubular portion and a second tubular portion, the first tubular portion being made from a relatively impermeable material and having a first tubular portion lumen, the first tubular portion having a proximal and a distal end, the second tubular portion having a second tubular portion lumen and an open end and a closed end, the open end disposed within the first tubular portion lumen at the distal end of the first tubular portion, the second tubular portion having a closed end disposed distally of the distal end of the first tubular portion, the second tubular portion being made of a porous material having a preselected microporosity that permits nonsteroidal anti-inflammatory agent having cyclooxygenase inhibitor action to flow through the second tubular portion lumen and out of the catheter through the second tubular portion into the hippocampus or lateral ventricle.

12. A catheter for conveying indomethacin into an hippocampus or lateral ventricle, the catheter having a distal and a proximal end, the catheter comprising:

a) a first tubular portion made from a relatively impermeable material, the first tubular portion having a first tubular portion lumen;

b) a second tubular portion having an open end disposed within the distal end of the first tubular portion lumen and a closed end disposed distally of the distal end of the first tubular portion lumen, the second tubular portion being made of a porous material having a preselected microporosity;

whereby indomethacin flows through the first tubular portion lumen and out of the catheter through the second tubular portion into the hippocampus or lateral ventricle.

13. The catheter of claim 12 wherein the porous material has a microporosity of less than or equal to 0.22 microns.

14. The catheter of claim 12 wherein the porous material is selected from the group of materials consisting of polyamide, polyethylene, polypropylene and hollow fiber polysulfone.

15. The catheter of claim 12 wherein the impermeable material of the first tubular portion is selected from the group of materials consisting of polyurethane, silicone and polyacrylonitrile.

16. The system of claim 12 wherein the impermeable material of the first tubular portion expands when exposed to a preselected solvent so that the internal diameter of the first tubular portion increases from a first internal diameter to a second internal diameter whereby the second tubular portion may be moved relative to the first tubular portion after the first tubular portion has been exposed to the preselected solvent and wherein the first tubular portion contracts when the solvent is removed from contact with the first tubular portion so that the first tubular portion returns to the first internal diameter.

17. The system of claim 12 wherein the impermeable material of the first tubular portion expands when heated so that the internal diameter of the first tubular portion increases from a first internal diameter to a second internal diameter whereby the second tubular portion may be moved relative to the first tubular portion after the first tubular portion has been exposed to heat and wherein the first tubular portion contracts when the first tubular portion is removed from contact with heat so that the first tubular portion returns to the first internal diameter.

18. The catheter of claim 12 wherein a portion of the distal end of the second tubular portion contains a radiographic marker.

19. The catheter of claim 12 wherein a portion of the distal end of the second tubular portion contains a nuclear magnetic resonance marker.

20. A catheter for conveying nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action into an hippocampus or lateral ventricle, the catheter having a distal and a proximal end, the catheter comprising:

a) a first tubular portion made from a relatively impermeable material, the first tubular portion having a first tubular portion lumen;

b) a second tubular portion having an open end disposed within the distal end of the first tubular portion lumen and a closed end disposed distally of the distal end of the first tubular portion lumen, the second tubular portion being made of a porous material having a preselected microporosity;

whereby nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action flows through the first tubular portion lumen and out of the catheter through the second tubular portion into the hippocampus or lateral ventricle.

21. A catheter comprising:

an elongated tubular portion having a tubular portion lumen, a proximal end and a distal end, the tubular portion terminating at the most distal end in a tip wherein the tubular portion expands in diameter in response to an external stimulus.

22. The catheter of claim 21 wherein the tubular portion is composed of a relatively impermeable material.

23. The catheter of claim 22 wherein the relatively impermeable material of the tubular portion is polyacrylonitrile.

24. The catheter of claim 21 wherein the tubular portion is composed of a tear resistant material.

25. The catheter of claim 24 wherein the tear resistant material is chosen from the group consisting of silicone elastomer and polyurethane.

26. The catheter of claim 21 wherein the tubular portion is made of a biocompatible material.

27. The catheter of claim 21 wherein the tip is rounded to minimize tissue disruption during insertion.

28. The catheter of claim 21 wherein the tubular portion has an externally tapered distal end surface to minimize tissue disruption during insertion.

29. The catheter of claim 21 wherein the tip has a generally tubular shape and fits snugly within the tubular portion lumen.

30. The catheter of claim 21 wherein the tip has a tip lumen aligned with and in fluid communication with the tubular portion lumen.

31. The catheter of claim 21 wherein the diameter of the tubular portion lumen and the external diameter of tip are the same.

32. The catheter of claim 21 wherein the tip is composed in part of a porous material chosen from the group consisting of polysulfone, polyethylene, polyamide, polypropylene and expanded polytetrafluoroethylene (ePTFE).

33. The catheter of claim 32 wherein the porous material of the tip extends along the entire length of the tip.

34. The catheter of claim 32 wherein the pore size of the porous material of the tip is approximately between 0.1-0.2 microns.

35. The catheter of claim 21 wherein the tip has at least one elution hole extending therethrough in fluid communication with the tubular portion lumen.

36. The catheter of claim 21 wherein the tubular portion is made of a relatively impermeable material such as polyacrylonitrile, polyethylene, polypropylene, or silicone elastomer.

37. The catheter of claim 21 further comprising means for locating the distal end of the catheter during a process of positioning the catheter.

38. The catheter of claim 37 wherein the means for locating is a radiopaque marker located on the distal end of the catheter.

39. The catheter of claim 38 wherein the marker comprises tantalum powder dispersed in a matrix of a biocompatible adhesive.

40. The catheter of claim 38 wherein the marker comprises barium powder dispersed in a matrix of a biocompatible adhesive.

41. The catheter of claim 38 wherein the marker comprises platinum powder dispersed in a matrix of a biocompatible adhesive.

42. The catheter of claim 38 wherein the marker comprises a semispherical portion having a cylindrical nipple emanating away from the semispherical portion.

43. A method of delivering indomethacin to a selected site within a hippocampus or latereral ventricle comprising the steps of:

a) providing a catheter having a first tubular portion that has a first tubular portion lumen and a second tubular portion partially disposed within the first tubular portion lumen;

b) adjusting the length of the second tubular portion extending from the first tubular portion lumen to conform to the dimensions of a selected site in an hippocampus or lateral ventricle;

c) placing the catheter in the hippocampus or lateral ventricle so that the second tubular portion is placed at the selected site in the hippocampus or lateral ventricle;

d) providing a source of indomethacin;

e) coupling the catheter and the source of indomethacin to a pump for delivering indomethacin from the source of indomethacin to the hippocampus through the catheter; and

f) actuating the pump to deliver the indomethacin to the hippocampus or lateral ventricle.

44. The method of claim 43 wherein the step of providing a catheter having a first tubular portion that has a first tubular portion lumen includes the step of:

a) making the first tubular portion of a material that increases in diameter when heated; and,

wherein the step of adjusting the length of the second tubular portion includes the steps of:

1) heating the first tubular portion until the diameter of the first tubular portion lumen increases in diameter a sufficient amount to enable relative sliding movement between the first tubular portion and the second tubular portion;

2) sliding the second tubular portion in the first tubular portion lumen relative to the first tubular portion to provide a preselected length of the second tubular portion extending beyond the end of the first tubular portion; and

3) cooling the first tubular portion until the first tubular portion and the second tubular portion are no longer capable of relative sliding movement.

45. The method of claim 43 wherein the step of providing a catheter having a first tubular portion that has a first tubular portion lumen includes the step of:

a) making the first tubular portion of a material that increases in diameter when exposed to a solvent; and,

wherein the step of adjusting the length of the second tubular portion includes the steps of:

1) exposing the first tubular portion to a solvent that increases the diameter of the first tubular portion lumen a sufficient amount to permit relative sliding movement of the second tubular portion in the first tubular portion lumen;

2) sliding the second tubular portion in the first tubular portion lumen to obtain a preselected length of the second tubular portion extending distally beyond the distal end of the first tubular portion; and

3) ceasing to expose the first tubular portion to the solvent whereby the diameter of the first tubular portion lumen decreases until relative sliding movement between the first tubular portion and the second tubular portion is prevented.

46. A method of delivering nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action to a selected site within a hippocampus or latereral ventricle comprising the steps of:

a) providing a catheter having a first tubular portion that has a first tubular portion lumen and a second tubular portion partially disposed within the first tubular portion lumen;

b) adjusting the length of the second tubular portion extending from the first tubular portion lumen to conform to the dimensions of a selected site in an hippocampus or lateral ventricle;

c) placing the catheter in the hippocampus or lateral ventricle so that the second tubular portion is placed at the selected site in the hippocampus or lateral ventricle;

d) providing a source of nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action;

e) coupling the catheter and the source of nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action to a pump for delivering nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action from the source of nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action to the hippocampus through the catheter; and

f) actuating the pump to deliver the nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action to the hippocampus or lateral ventricle.

47. A method of making a catheter comprising the steps of:

providing a tubular body made of a tear resistant material that expands in the presence of a select external stimulus, the tubular body having a tubular body lumen with a diameter;

exposing the tubular body to the external stimulus that causes the material of the tubular body to expand whereby the tubular body expands;

placing a tip in the tubular body lumen, the tip having an outside diameter at least equal to the inside diameter of the tubular body lumen when the tubular body is not exposed to the select external stimulus;

moving the tip relative to the tubular body to achieve a desired configuration between the tip and the tubular body; and,

halting the exposure of the select external stimulus to the tubular body whereby the tubular body returns to its original size.

48. The method of claim 47 wherein the material that expands in the presence of a select external stimulus is chosen from the group consisting of silicone elastomer or polyurethane.

49. The method of claim 47 wherein the step of providing a tubular body includes the step of making the tubular body of a material that increases in diameter when heated;

wherein the step of placing a tip in the tubular body lumen includes the step of heating the tubular body until the diameter of the tubular body lumen increases in diameter a sufficient amount to enable relative sliding movement between the tubular body and the tip as the tip is placed in the tubular body lumen; and, wherein the step of halting the exposure of the select external stimulus to the tubular body includes the step of cooling the tubular body until the tubular body and the tip are no longer capable of relative sliding movement.

50. The method of claim 47 wherein the step of providing a tubular body includes the step of making the tubular body of a material that increases in diameter when exposed to a solvent; wherein the step of placing a tip in the tubular body lumen includes the step of exposing the tubular body to the solvent until the diameter of the tubular body lumen increases in diameter a sufficient amount to enable relative sliding movement between the tubular body and the tip as the tip is placed in the tubular body lumen; and, wherein the step of halting the exposure of the select external stimulus to the tubular body includes the halting the exposure of the tubular body to the solvent until the tubular body and the tip are no longer capable of relative sliding movement.

51. The method of claim 47 wherein the step of exposing the tubular body to the external stimulus includes the step of exposing the tubular body to a solvent.

52. The method of claim 51 wherein the step of halting the exposure of the select external stimulus to the tubular body includes evaporating the solvent.

53. The method of claim 47 further comprising the steps of:

providing a connecting catheter for connecting the proximal end of the catheter to a source of indomethacin.

54. The method of claim 47 further comprising the steps of:

providing a connecting catheter for connecting the proximal end of the catheter to a source of nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action.

55. A method of manufacturing a catheter comprising the steps of:

a) forming a first tubular portion of a relatively impermeable material, the first tubular portion formed having a lumen with a diameter;

b) forming second tubular portion of a porous material;

c) partially disposing the second tubular portion within the lumen;

d) adjusting the length of the second tubular portion to conform to the dimensions of a selected site in an hippocampus or lateral ventricle; and

e) establishing a near zero tolerance fit between the overlap of the second tubular portion and the first tubular portion.

56. The method of claim 55 wherein the step of forming a first tubular portion of a relatively impermeable material includes the step of forming the first tubular portion of a material that increases in the diameter of the lumen when the first tubular portion is heated; and, wherein the step of adjusting the length of the second tubular portion comprises the steps of:

a) heating the first tubular portion until the diameter of the lumen increases in diameter a sufficient amount to enable relative sliding movement between the first tubular portion and the second tubular portion;

b) sliding the second tubular portion in the lumen relative to the first tubular portion to provide a preselected length of the second tubular portion that extending distally beyond the distal end of the first tubular portion; and

c) cooling the first tubular portion until the first tubular portion and the second tubular portion are no longer capable of relative sliding movement.

57. The method of claim 55 wherein the step of forming a first tubular portion of a relatively impermeable material includes the step of forming the first tubular portion of a

material that increases in the diameter of the lumen when the first tubular portion is exposed to a solvent; and, wherein the step of adjusting the length of the second tubular portion comprises the steps of:

a) exposing the first tubular portion to a solvent that increases the diameter of the lumen a sufficient amount to permit relative sliding movement of the second tubular portion in the lumen;

b) sliding the second tubular portion in the lumen to obtain a preselected length of the second tubular portion extending distally beyond the distal end of the first tubular portion; and

c) ceasing to expose the first tubular portion to the solvent whereby the diameter of the first tubular portion decreases until relative sliding movement between the first tubular portion and the second tubular portion is prevented.

58. A method of treating Alzheimer's disease comprising the steps of:

implanting the distal end of a catheter having a distal end and a proximal end in a patient's hippocampus or lateral ventricle;

attaching the proximal end of the catheter to a source of indomethacin;

infusing indomethacin through the catheter to exit the distal end of the catheter in the patient's hippocampus or lateral ventricle.

59. The method of claim 58 wherein the step of implanting the distal end of a catheter includes the step of accessing the hippocampus through a posterior occipital lobe.

60. The method of claim 58 wherein the step of implanting the distal end of a catheter includes the step of anteriorally accessing the lateral ventricle through the frontal lobe.

61. The method of claim 58 wherein the step of implanting the distal end of a catheter includes the step of posteriorally accessing the lateral ventricle through the occipital lobe.

62. The method of claim 58 wherein the step of implanting includes the steps of:

introducing a trocar into the patient's hippocampus or lateral ventricle;

passing the catheter through the trocar so that the distal end of the catheter leaves the trocar and enters the hippocampus or lateral ventricle;

removing the trocar leaving the catheter in place.

63. The method of claim 58 wherein the step of implanting includes the step of:

introducing a catheter containing a stylet through a selected lobe to the patient's hippocampus or lateral ventricle;

removing the stylet leaving the catheter in place.

64. A method of treating Alzheimer's disease comprising the steps of:

implanting the distal end of a catheter having a distal end and a proximal end in a patient's hippocampus or lateral ventricle;

attaching the proximal end of the catheter to a source of nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action;

infusing nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action through the catheter to exit the distal end of the catheter in the patient's hippocampus or lateral ventricle.

Abstract of the Disclosure

A method and apparatus for treating Alzheimer's disease is disclosed. The method comprises delivering indomethacin or nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action directly to the hippocampus or the lateral ventricle through an implanted catheter. The catheter has a flexible distal end that is implanted directly in the hippocampus or lateral ventricle as the preferred embodiment. The distal end has either a porous tip or a closed end. Where the distal end is closed, or a plurality of elution holes are present indomethacin is delivered to the hippocampus or lateral ventricle through either the porous tip or the elution holes. The catheter is part of a system for delivering indomethacin or nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action to the hippocampus or lateral ventricle that includes a pump coupled to the catheter for delivering the indomethacin or nonsteroidal anti-inflammatory agents having cyclooxygenase inhibitor action through the catheter to the hippocampus or lateral ventricle.

ATTACHMENT 5

SPE SCHULTZ'S PRESENTATION

Patenting Interfering RNA

J. Douglas Schultz

SPE Art Unit 1635

(571) 272-0763

James.Schultz@uspto.gov

35 U.S.C. 112, first paragraph, Enablement

RNAi Predictability

- High *in vivo* unpredictability due to general lack of knowledge regarding efficacy and *in vivo* target site determination, and delivery issues, methods particularly.

- Delivery, Delivery, Delivery

- To date only one human antisense with FDA approval.
  - no FDA approval for any siRNA, miRNA, ribozyme, etc.